No new matter has been introduced by the amendments. Support for amendments to claim 1 may be found in claims 2 and 3. Further support to the property that an immune response is elicited to epitopes comprising the non-reducing terminal glucuronic acid or unsaturated glucuronic acid residues of the hyaluronic acid moieties is found on page 6, ln. 13 – page 10, ln. 21.

Specification - Informalities

4.

(a) The use of trademarks in the instant specification has been objected to. Applicants have amended the specification to capitalize the recitations in order to address the Examiner's concerns. Reconsideration and withdrawal of specification objection is respectfully requested.

(b) The Examiner has objected to the specification as failing to provide proper antecedent basis for the claimed subject matter. Applicants assert, however, that the specification does provide proper antecedent basis for the subject matter as claimed in claim 1, specifically the recitation "immunologically-suitable" polypeptide carrier. The Examiner's attention is respectfully directed to the MPEP 2173.05(e) under "A claim term which has no antecedent basis in the disclosure is not necessarily indefinite." The MPEP states on page 2100-200:

> The mere fact that a term or phrase used in the claim has no antecedent basis in the specification disclosure does not mean, necessarily, that the term or phrase is indefinite. There is no requirement that the words in the claim must match those used in the specification disclosure. (emphasis added)

Since the MPEP states that the exact term or phrase used in the claim is not required in the specification, the instant specification need only define "immunologically-suitable" polypeptide carriers in a manner that one skilled in the art would understand. "Immunologically-suitable" polypeptide carriers are described on page 11, lines 10-22 of the instant specification as "any physiologically tolerated protein or polypeptide which evokes a T cell dependent response when

coupled to LMW-HA." Also, the Summary of the Invention of the instant specification describes LMW-HA conjugates that are immunogenic in mammals and elicit antibodies that are cross-reactive with groups A and C streptococci (pg. 3, lns. 20-22). As such, the conjugates comprising polypeptide carriers are immunologically-suitable and are described in the instant specification in a manner that one skilled in the art would understand "immunologically-suitable" polypeptide carriers to be polypeptides that elicit an immunological response. Therefore, since there is no requirement that the claimed words must match those used in the specification and that the recitation "immunologically-suitable polypeptide carrier" is clearly understood and supported by the specification, applicants respectfully request reconsideration and withdrawal of this objection.

35 U.S.C. §112, Second Paragraph

5. Claims 2-18 and 29 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

(a) Claim 2, which depends from claim 1, stands rejected to for allegedly lacking proper antecedent basis for the recitation "the hyaluronic acid molecules." Applicants respectfully disagree with this rejection. However, where appropriate, applicants have amended the claims to address the Examiner's concerns. In particular, claim 2 has been cancelled and the subject matter of claim 2 has been incorporated into claim 1. The subject matter of claim 2 and claims 1, 3-9, 13 have been amended to delete the term "hyaluronic acid molecules" and recite "hyaluronic acid moiety." Reconsideration and withdrawal of this §112, second paragraph rejection is respectfully requested.

(b)-(e) The Examiner has rejected claims 4-7 as being confusing and/or redundant in the recitation of "at least ... or greater." In order to expedite prosecution of this application, claims 4-7 have been amended to delete the phrase "or greater." This amendment should not be construed as changing the scope of the claimed invention. Reconsideration and withdrawal of this §112, second paragraph rejection is respectfully requested.

(f) Claims 4-7 stand rejected for allegedly lacking proper antecedent basis for the recitation "the low molecular weight hyaluronic acid fragments," where claims 4-7 depend from claim 3 which does not recite any hyaluronic acid "fragments." In order to address the Examiner's concerns and to expedite prosecution of this application, claim 3 has been amended to recite "wherein the hyaluronic acid moiety." Applicants respectfully direct the Examiner's attention to page 7, line 1 through page 8, line 9, and page 11, line 23 through page 12, line 8 of the instant specification, where either native HA or low molecular weight HA and fragments thereof, are disclosed as being useful for preparing conjugates. Furthermore, "moiety" is defined by *Hawley's Condensed Chemical Dictionary, Twelfth Edition* (Revised by Richard J. Lewis, Sr., Van Nostrand Reinhold Company, New York, NY, 1993) as: an indefinite portion of a sample. Thus, one skilled in the art would understand the term "hyaluronic acid moiety" to mean the poly-glucuronic acid portion or part of the macromolecular conjugate structure. Reconsideration and withdrawal of this §112, second paragraph rejection is respectfully requested.

(g) Claim 8 stands rejected as allegedly being vague and indefinite in the recitation of "about at least about." Applicants respectfully traverse this rejection. However, claim 8 has been amended to address the Examiner's concerns. In particular, the recitation "hyaluronic acid is about at least about" has been amended to read "hyaluronic acid moiety is at least about." Applicants respectfully request reconsideration and withdrawal of this §112, second paragraph rejection.

(h) Claim 11 stands rejected for allegedly being vague and indefinite as to the process encompassed by "deriving." Further, the Examiner has rejected claim 11 for allegedly being unclear as to whether the immunogenic polypeptide is the homologous polypeptide isolated from the recited microorganisms. Applicants respectfully disagree, however, claim 11 has been amended to recite, for example, "a streptococcal immunogenic polypeptide" instead of "an immunogenic polypeptide derived from streptococci." Reconsideration and withdrawal of this §112, second paragraph rejection is respectfully requested.

(i) Claim 13 stands rejected for being indefinite in the recitation "conjugate is directly linked," because the Examiner contends that it is unclear what the conjugate is linked to.

Applicants respectfully traverse this rejection, but have amended the claim in order to address the Examiner's concerns. Applicants respectfully direct the Examiner's attention to page 10, line 23 through page 11, line 8 where a carrier polypeptide or protein is bound to at least one low molecular weight hyaluronic acid fragment. In particular, claim 13 has been amended to recite "hyaluronic acid, or fragments thereof, is directly linked to the immunologically-suitable polypeptide carrier." Reconsideration and withdrawal of this §112, second paragraph rejection is respectfully requested.

(j) Claim 16 stands rejected for having a grammatical error. In order to expedite prosecution of this application, applicants have amended the claim to replace "bacteria is" with --bacterium is -- as suggested by the Examiner. Applicants respectfully request reconsideration and withdrawal of this §112, second paragraph rejection.

(k) The term "effective" in claim 29 is objected to by the Examiner as allegedly rendering the claim indefinite. Applicants respectfully disagree, but in order to expedite prosecution of this application, claim 29 has been amended to address the Examiner's concerns by deleting the recitation "effective levels." Reconsideration and withdrawal of this §112, second paragraph rejection is respectfully requested.

(l) Claims 3-18 and claim 29, depending from claim 2, stand rejected for being indefinite because base claim 2 is allegedly indefinite. Applicants have cancelled claim 2 and amended claim 3 to be dependent from claim 1, thus obviating this ground of rejection. Therefore, applicants request withdrawal of this ground of rejection. Reconsideration and withdrawal of this §112, second paragraph rejection is respectfully requested.

35 U.S.C. §102

7. Claim 1 stands rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Simon et al. (WO 00/12122), or Pierschbacher, et al. (U.S. 5,955,578), or Rhee, et al. (U.S. 5,510,418). Applicants respectfully disagree with this ground of rejection.

The Examiner asserts that the evidentiary references disclose immunogenic conjugate molecules comprising hyaluronic acid bound to immunologically-suitable polypeptide

carriers encompassed by the claimed methods. Applicants respectfully disagree with the Examiner's grounds or rejection.

The Simon, et al. publication reports low molecular weight fragments of hyaluronic acid which can be used with an antigen, peptide or carrier system for use in immunotherapy. Applicants specifically direct the Examiner's attention to page 22, ln. 20 – page 23, ln. 19 of Simon, where the vaccine comprises any antigen or peptide which elicits an immune response present preferably in the same solution as the hyaluronic acid fragments, where it is also possible to administer the antigen or peptide separately from the low molecular weight hyaluronic acid fragments. In contrast, the claimed invention is directed to an immungenic conjugate, where the low molecular weight hyaluronic acid fragment at the non-reducing terminal end elicits an immune response. In order to expedite prosecution of this application, applicants have amended independent claim 1 to address the Examiner's concerns. The limitations of claims 2 and 3 have been incorporated into claim 1. Specifically, the characteristics that greater than 50% of the hyaluronic acids of the claimed hyaluronic acid conjugates have a non-reducing terminal glucuronic acid and/or unsaturated glucuronic acid residue which induce an immune response and that the hyaluronic acid moieities are low molecular weight hyaluronic acid with a molecular weight of about 400 Kd or less and a molecular weight of about 600 daltons or more. These properties are preferred for achieving an immune response as described in the instant specification on page 12, lns. 9-20. Therefore, claim 1 as amended is not anticipated by Simon, et al.

Pierschbacher, et al. reports a conjugate comprising a synthetic polypeptide and a biodegradable polymer, such as hyaluronic acid. Pierschbacher, et al. simply reports a conjugate for wound healing which acts as a temporary replacement matrix. The Pierschbacher, et al. reference does not disclose the conjugate of claim 1 as amended. In fact, the method of preparing the conjugate as described by Pierschbacher (col. 5, lns 43-59; Example II) would not result in low molecular weight hyaluronic acid moieties as claimed in the instant specification. Specifically, Pierschbacher, et al. does not report hyaluronic acid conjugates having greater than 50% of the hyaluronic acid molecules with a nonreducing terminal glucuronic acid and/or unsaturated glucuronic acid residue which induce an immune response and that the hyaluronic

acid moieities are low molecular weight hyaluronic acid with a molecular weight of about 400 Kd or less and a molecular weight of about 600 daltons or more. Therefore, claim 1 is not anticipated by Pierschbacher, et al.

Rhee, et al. reports a non-immunogenic composition comprising covalently bound glycosaminoglucans, such as hyaluronic acid, and hydrophilic synthetic polymers. Rhee, et al. reports a composition that does not elicit an immune response. Specifically, the Examiner points to the abstract where "pharmaceutically acceptable, nonimmunogenic compositions are formed by covalently binding glycosaminoglycans or derivatives thereof, to hydrophilic synthetic polymers via specific types of chemical bonds to provide biocompatible conjugates." The conjugates as reported by Rhee, et al. "are useful in dermal wound healing and cardiovascular applications where immunological reactions are to be minimized or blood coagulation is to be avoided" (col. 5, lines 25-27). Rhee's conjugates specifically are designed to be non-immunogenic. Even with the addition of a cytokine as reported in the abstract, the purpose of Rhee's conjugates is not to trigger an immune response. In fact, claim 1 of the '418 patent specifically claims "a biocompatible, biologically inert conjugate comprising a chemically derivatized glycosaminoglycan chemically conjugated to a synthetic hydrophilic polymer" (emphasis added). The non-immunogenic nature of the Rhee products confers a fundamental difference between the products referred to by Rhee and applicants' claimed invention. Thus, Rhee, et al. does not anticipate the immunogenic conjugate of the claimed invention.

None of the references, Simon, et al., Pierschbacher, et al., and Rhee, et al., anticipate the claimed invention as reported in amended claim 1. Applicants respectfully request reconsideration and withdrawal of this §102 rejection.

8. Claim 1 has also been rejected under 35 U.S.C. §102(b) as being anticipated by Fillit, et al. (J. Exp. Med. 164:762-776, 1986) (Fillet, et al. 1986) as evidenced by Nebinger, et al. (J. Chromatol. 320:351-359, 1985) (Nebinger, et al. 1985). Applicants respectfully disagree.

Fillit, et al. reports the immunogenicity of hyaluronic acid by immunizing rabbits with encapsulated streptococci. This reference simply confirms the presence of anti-hyaluronate antibodies. Conjugation of hyaluronate to BSA or biotin as reported by Fillit, et al. is essentially

for binding hyaluronate to the ELISA plates. Specifically, Fillet states "Intact streptococcal hyaluronate was conjugated to BSA. This was done to assure binding of the hyaluronate to the ELISA plates via the protein portion of the conjugate" (pg. 764, lns. 9-12) and 41-43). The Examiner contends that the immunogenic function of the conjugate is inherent in the conjugate. However, the Fillit does not disclose the properties as claimed in amended claim 1, i.e., greater than 50% of the hyaluronic acids of the claimed hyaluronic acid conjugates have a non-reducing terminal glucuronic acid and/or unsaturated glucuronic acid residue which induce an immune response and that the hyaluronic acid moieities are low molecular weight hyaluronic acid with a molecular weight of about 400 Kd or less and a molecular weight of about 600 daltons or more. The Fillit, et al. reference, therefore, does not anticipate the immunogenic conjugate as reported in amended claim 1.

The Examiner contends that Nebinger, et al. (1985) shows that every element of the claimed subject matter is disclosed by Fillit, et al. However, Nebinger, et al. (1985) simply reports separating oligosaccharides of hyaluronic acid using various chromatography methods. This reference does not disclose immunological conjugates comprising hyaluronic acid fragments and an immunologically-suitable polypeptide carrier. Nebinger, et al. does not teach how one skilled in the art would prepare an immunological conjugate comprising hyaluronic acid and a polypeptide carrier. In fact, Nebinger, et al. reports the opposite, i.e. how to separate hyaluronate oligosaccharides using chromatography techniques. The skilled artisan would not be motivated from reading Nebinger, et al. to prepare conjugates as claimed in the instant application.

Fillit, et al. does not anticipate the claimed invention as reported in amended claim 1. Applicants respectfully request reconsideration and withdrawal of this §102 rejection.

35 U.S.C. §103

10. Claims 1-10 and 13-18 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Fillit, et al. (1986), in view of Nebinger, et al. (Nebinger, et al., 1983), or Nebinger, 1985, or Shimada, et al. (J. Biochem (Tokyo) 96:721-725, 1984), or Ulrich, et al. (*Hoppe-Seyler's Z. Physiol. Chem.* 360:1457-1463, 1979, abstract). As an initial matter, with

respect to the composition claims, the combination of references relied upon by the Examiner, fails to teach or suggest applicants' claimed compositions having the percent glucuronic acid content of the hyaluronic acid (HA) or molecular weight of HA as presently stated in claims 1 and 3. Further, the Examiner has used hindsight to amass the cited art (which does not teach or make obvious applicants' invention) as there is no motivation to combine these particular references in this particular fashion. Applicants respectfully traverse this rejection.

The Examiner contends that Fillit, et al. provides the motivation to prepare conjugate compositions comprising hyaluronic acid conjugated to an immunologically-suitable polysaccharide carrier, where more than 50% of the hyaluronic acid molecules have a non-reducing terminal glucuronic acid and/or unsaturated glucuronic acid residue. However, Fillit, et al., as the Examiner admits, is "silent about the molecular weight of the hyaluronic acid of claim 3 (and depending claims) present in their conjugate, or of the percent glucuronic acid content of the HA" (paper no. 6, pg. 8, lns. 12-13). The Examiner further contends that Fillit, et al. teaches the need to reduce the viscosity of hyaluronate and to render it manageable for further manipulation. Further, the Examiner has used hindsight in rejecting these claims regarding the immunogenic conjugate comprising HA and an immunologically-suitable polypeptide carrier of the claimed invention. The art has been unpredictable in showing that HA is immunogenic. Fillit, et al. report that "A number of investigators have attempted to show that hyaluronate is immmunogenic. In general, these studies have failed to show that immunogenicity of hyaluronate, despite the variety of methods used of immunoization, including the use of hyaluronate conjugated to BSA as a hapten-carrier immunogen (Fillet, et al., pg. 762, lns. 1-6). In fact, the art cited by the Examiner actually teaches away from applicants' invention of using a carrier that elicits an immune response by reporting the use of BSA as a carrier, where BSA is not used to elicit an immune response, but is used only to "assure binding of the hyaluronate to the ELISA plates via the protein portion of the conjugate" (Fillit, et al., pg. 764, lns. 9-12).

According to the Examiner, Fillit, et al. reports that enzymatic treatment with testicular hyaluronidase exposes hidden antigenic sites of hyaluronate that contain terminal glucuronic acid (pg 763 and 762), where the hyalurondidase –hydrolyzed hyaluronate oligosaccharides are used for conjugation (page 763). However, Fillit, et al., in view of the

combination of references, does not motivate the skilled artisan to modify the teachings of Fillit, et al. in order to obtain the conjugate composition of claims 1–10 and claims 13-18. The proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, such that the teachings of the references are not sufficient to render the claims prima facie obvious. In *re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959). As previously discussed, Fillit, et al. reports compositions comprising HA conjugated to BSA or biotin for the sole purpose of attaching the HA to an ELISA plate (pg. 764, lns. 9-12 and 41-43). Nothing in Fillet, et al. would provide any motivation to one skilled in the art to prepare conjugates as vaccines suitable for eliciting a T cell dependent response. Thus, the skilled artisan would have no motivation to modify the conjugate molecule as reported by Fillet, et al. to have an immunologically-suitable polypeptide carrier that is claimed in claim 1. The art has been unpredictable in showing that HA is immunogenic (Fillit, et al. pg. 762, lns. 1-6). In fact, the art cited by the Examiner actually teaches away from applicants' invention of using a carrier that elicits an immune response by reporting the use of BSA as a carrier, where BSA is not used to elicit an immune response, but is used only to "assure binding of the hyaluronate to the ELISA plates via the protein portion of the conjugate" (Fillit, et al., pg. 764, lns. 9-12).

Oligosaccharides of HA having low molecular weight are argued by the Examiner to have been routinely produced by those skilled in the art. The Examiner contends that Nebinger, et al. (1985) teaches odd- and even- numbered oligosaccharides of HA of up to decasaccarides containing glucuronic acid at the non-reducing terminus.

Nebinger, et al. (1983) reports high-performance liquid chromatographic analysis of hyaluronate oligosaccharides. The Nebinger, et al. reference further reports analyzing even-numbered and odd-numbered oligosaccharides of up to octasaccharides derived from hyaluronic acid. However, Nebinger, et al. does not teach or suggest the conjugate composition nor provides any guidance as to how one skilled in the art would prepare immunogenic conjugate molecules where greater than 50% of the hyaluronic acid molecules have non-reducing terminal glucuronic acids and/or unsaturated glucuronic acid residues and the hyaluronic acid has a molecular weight ranging from between 600 daltons and 400 Kd and an immunologically-suitable polysaccharide carrier. Since Nebinger, et al. (1983) does not teach or suggest the

subject matter of either claim 1 or claim 3, dependent claims 13-18 (i.e., depend from claim 3), are also not taught or suggested by Nebinger, et al.

Once again, the Examiner contends that references reporting oligosaccharides of hyaluronic acid of varying lengths contribute to teaching and suggesting the conjugate molecules of the claimed invention. Applicants disagree with the Examiner's contention because the compositions reported in the combination of references cited by the Examiner are not "immunogenic conjugate molecules" as that term is used in the present application and therefore do not anticipate or make obvious applicants' claims.

Shimada, et al. simply reports thin-layer chromatographic analysis of hyaluronate oligosaccharides. The Shimada, et al. reference further reports separating even-numbered and odd-numbered oligosaccharides by thin-layer chromatography (TLC). However, Shimada, et al. does not provide any guidance as to how the skilled artisan would prepare immunogenic conjugate molecules comprising hyaluronic acid and an immunologically-suitable polypeptide carrier, where greater than 50% of the hyaluronic acid molecules have non-reducing terminal glucuronic acids and/or unsaturated glucuronic acid residues, and the hyaluronic acid has a molecular weight ranging from between 600 daltons and 400 Kd. In fact, Shimada, et al. simply reports "the application of TLC to the separation of several series of odd and even-numbered hyaluronate oligosaccharides" (pg. 721, col. 2, last paragraph before "Materials and Methods"). The Shimada, et al. reference does not state the molecular weight of the hyaluronic acid present, or the percent glucuronic acid content of the hyaluronic acid. The Examiner argues that by describing odd- and even- numbered hyaluronic acid oligosaccharides, Shimada, et al. implies low molecular weight hyaluronic acid and the conjugate molecules as claimed in the present application. Even assuming that Shimada, et al. reported low molecular weight hyaluronic acid, the information does not teach or suggest the applicants' claimed invention, nor does it provide motivation to one skilled in the art to use low molecular weight hyaluronic acid to produce vaccines. Since Shimada, et al. does not teach or suggest the subject matter of either claim 1 or claim 3, dependent claims 13-18 (i.e., depend from claim 3), are also not taught or suggested by Shimada, et al.

Furthermore, the Examiner contends that Ulrich, et al. teaches oligosaccharides of hyaluronic acid, including a tetrasaccharide, and therefore a low molecular weight hyaluronic acid. However, Ulrich, et al. do not teach or suggest a conjugate molecule comprising hyaluronic acid and an immunologically-suitable polypeptide carrier. A skilled artisan would not be motivated from reading the Ulrich, et al. abstract to prepare the claimed conjugate molecule since it simply reports degrading even-numbered oligosaccharides from hyaluronic acid with either D-glucuronic acid or N-acetylglucosamine using specific lyases. Thus, the claimed invention is not taught or suggested by Ulrich, et al.

The Examiner contends that Fillit, et al. reports conjugate compositions comprising HA and BSA. Nebinger, et al. (1983, 1985), Shimada, et al., and Ulrich, et al. are reported by the Examiner as related to the low molecular weight of hyaluronic acid. However, none of Nebinger, et al. (1983, 1985), Shimada, et al., or Ulrich, et al. when combined with Fillit, et al. either individually or in combination, remedy the deficiencies of Fillit, et al. as a prior art reference. That is, the combination of cited art does not teach or suggest the possibility that hyaluronic acid and immunologically-suitable polypeptide carriers, as taught by applicants' invention, could be used to produce the novel immunogenic conjugate molecules of the invention.

Fillit, et al., Nebinger, et al. (1983), Nebinger, et al. (1985), Shimada, et al., and Ulrich, et al., either alone or in combination, do not make obvious the claimed invention as reported in claim 1 or 3, or depending claims 13-18. Applicants respectfully request reconsideration and withdrawal of this §103 rejection.

11. Claims 3, 11, 12, and 29 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Fillit, et al. as modified by Nebinger, et al. (1983, 1985), or Shimada, et al., or Ulrich, et al. as applied to claims 2 and 1 above, and further in view of Blake, et al. (US 5,439,808) and Swain, et al. (US 6,054,127; not Philip, et al. as the Examiner has stated). The Examiner contends that it would have been obvious to one of ordinary skill in the art to replace bovine serum albumin in the Fillet, et al. conjugate as modified by Nebinger, et al. (1983 or 1985) or Shimada, et al. or Ulrich, et al. with Blake's meningococcal porin to produce the conjugate of the

instant invention with a reasonable expectation of success. Further, the Examiner contends that the skilled artisan "would have been motivated to produce the instant invention for the expected benefit of avoiding the generation of anti-BSA antibodies in humans that have the potential to cause adverse responses, as taught by Philip et al. [sic; Swain, et al.]" (pg. 10 lns. 11-19). However, the Examiner readily admits that Fillet, et al., as modified by Nebinger, et al. (1983 or 1985) or Shimada, et al. or Ulrich, et al., "do not teach neisserial porin or a meningococcal protein as the immunologically-suitable polypeptide in the conjugate" (Paper No. 6, pg. 9, ln. 29 through pg. 10, ln. 2). The Examiner uses Blake, et al. and Swain, et al. to show that the use of meningococcal protein or porin in producing polysaccharide conjugates is commonly known in the art. Applicants respectfully traverse this ground of rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, (Fed. Cir. 1991).

The combination of Fillet, et al., Nebinger, et al. (1983 or 1985), Shimada, et al., Ulrich, et al., Blake, et al., and Swain, et al. fails to teach or suggest all of the claim limitations, and further, the references are impermissibly combined. There is no teaching or suggestion in the combination of references of a conjugate molecule comprising greater than 50% of the hyaluronic acids of the claimed hyaluronic acid conjugates have a non-reducing terminal glucuronic acid and/or unsaturated glucuronic acid residue which induce an immune response and that the hyaluronic acid moieities are low molecular weight hyaluronic acid with a molecular weight of about 400 Kd or less and a molecular weight of about 600 daltons or more. There is no teaching or suggestion in the combination of the references of such an immunogenic conjugate. Furthermore, the art has previously failed to consider HA as an immunogen. As

discussed above, applicants respectfully direct the Examiner's attention to page 762, lines 1-6 of Fillit, et al., which emphasizes that the art has failed to show HA as an immunogen.

Not only does the combination of Fillit, et al., Nebinger, et al. (1983 or 1985), Shimada, et al., Ulrich, et al., Blake, et al., and Swain, et al. fail to teach or suggest all of the claim limitations, the references are impermissibly combined as the proposed modification would change the principal operation of each reference. See *In re Rahi*, 270 F.2d 810 (CCPA 1959). Fillet, et al. reports that "streptococcal hyaluronate (fraction IA) was conjugated to BSA...to assure binding of the hyaluronate to the ELISA plates"(pg. 764, lns. 9-12) and that "the reactivity to hyaluronate-BSA observed was not due to reactivity to BSA" (pg. 766, lns. 1-2). The Examiner merely relies on Swain as teaching the undesirability of using BSA in human vaccines. Fillit, et al., however, reports that BSA is simply used for attaching the hyaluronate to ELISA plates and BSA does not serve to induce an immune response. In contrast, the instant specification describes on page 11, lines 10-12, "the polypeptide component of the conjugate molecules of the invention may be any physiologically tolerated protein or polypeptide which evokes a T cell dependent response when coupled to LMW-HA." Therefore, the carrier must contribute to a T-cell response, regardless of the immune response to hyaluronic acid. Thus, the Examiner' s suggested combination of Fillit, et al. and Swain, et al. would require a substantial change in the basic principles under which each of the Fillit, et al. and Swain, et al. references were designed to operate. This is impermissible. Id. 270 F.2d at 813.

In addition, the combination of Fillit, et al. and Blake, et al. fails to teach or suggest applicants' claimed immunogenic conjugate. The Examiner contends that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to replace bovine serum albumin in the Fillits' [sic] (1986) conjugate...with Blake's meningococcal porin to produce the conjugate of the instant invention" (Paper No. 6, pg. 10, lns. 11-14). Applicants traverse the ground of rejection as Blake, et al. merely provides another example of a carrier protein. The combination of publications as relied on by the Examiner, however, is improper because they do not themselves provide any motivation for their combination. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. In re Mills, 916

F.2d 680 (Fed. Cir. 1990). In fact, Fillit, et al. teaches away from the combination because it describes that its carrier does not induce an immune response and also reports that the BSA carrier is simply used as an attachment tool for binding BSA to ELISA plates. Moreover, Fillit, et al.fails to teach the use of hyaluronic acid as an immunogen. As stated above, Blake, et al. and Swain, et al. are simply examples of another protein carrier, yet neither of these references, either alone or in combination with the cited references, teaches the specifically claimed conjugate. Therefore, in light of the arguments presented above, applicants respectfully request reconsideration and withdrawal of this ground of rejection.

Therefore, Fillet, et al., Nebinger, et al. (1983 or 1985), Shimada, et al., Ulrich, et al., Blake, et al., or Swain, et al., neither alone or in combination, teach, suggest, or obviate to one skilled in the art the immunogenic conjugate molecules comprising hyaluronic acid covalently bound to an immunologically-suitable polypeptide carrier as claimed in the instant application. Thus, applicants respectfully request reconsideration and withdrawal of this §103 rejection.

Objections

12. Claim 9 has been objected to for the recitation "hyaluronic acid possess" as opposed to the correct grammatical phrase "hyaluronic acid possesses." The claim has been amended as suggested by the Examiner. Applicants respectfully request reconsideration and withdrawal of this grammatical error objection.

CONCLUSION

As required by 37 C.F.R. 1.121, "marked up" versions of the amended claims and of the replacement paragraphs of the specification are attached herewith with additions indicated by underlining and deletions by brackets.

Allowance of the pending claims is respectfully requested. Early and favorable action by the Examiner is earnestly solicited.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for the timely consideration of this amendment under 37 C.F.R. §§ 1.16 and 1.17, or credit any overpayment to Deposit Account No. 13-4500, Order No. 3842-4050.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition and for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 13-4500, Order No. 3842-4050. A DUPLICATE COPY OF THIS SHEET IS ATTACHED.

Respectfully submitted,

MORGAN & FINNEGAN, L.L.P.

Dated: February 6, 2003

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400kD – 600kD

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please cancel claims 2 and 3 without prejudice.

IN THE CLAIMS

1. (amended) An immunogenic conjugate molecule comprising hyaluronic acid moieties covalently bound to an immunologically-suitable polypeptide carrier, wherein greater than about 50% of the hyaluronic acid moieties possess a non-reducing terminal glucuronic acid and/or unsaturated glucuronic acid residue, wherein the hyaluronic acid moieties are low molecular weight hyaluronic acid with a molecular weight of about 400 kD or less and a molecular weight of about 600 daltons or more, and said immunogenic conjugate induces an immune response to epitopes comprising the non-reducing terminal glucuronic acid or unsaturated glucuronic acid residues of said hyaluronic acid moieties.

4. (amended) The immunogenic conjugate according to claim 1[3], wherein at least 90% [or greater]of the low molecular weight hyaluronic acid moieties[fragments] possess a nonreducing terminal glucuronic acid and/or unsaturated glucuronic acid residue.

5. (amended) The immunogenic conjugate according to claim 1[3], wherein at least 95% [or greater]of the low molecular weight hyaluronic acid moieties[fragments] possess a nonreducing terminal glucuronic acid and/or unsaturated glucuronic acid residue.

6. (amended) The immunogenic conjugate according to claim 1[3], wherein at least 98% [or greater]of the low molecular weight hyaluronic acid moieties[fragments] possess a nonreducing terminal glucuronic acid and/or unsaturated glucuronic acid residue.

7. (amended) The immunogenic conjugate according to claim 1[3], wherein at least 99% [or greater]of the low molecular weight hyaluronic acid moieties[fragments] possess a nonreducing terminal glucuronic acid and/or unsaturated glucuronic acid residue.

8. (amended) The immunogenic conjugate according to claim 1[3], wherein the low molecular weight hyaluronic acid moieties are [about] at least about 4 glycosyl residues in size.

9. (amended) The immunogenic conjugate according to claim 1[3], wherein the low molecular weight hyaluronic acid moieties possess about 2 to about 20 disaccharide subunits.

10. (amended) The immunogenic conjugate according to claim 9, wherein the low molecular weight hyaluronic acid moieties possess about 2 to about 10 disaccharide subunits.

11. (amended) The immunogenic conjugate according to claim 1[3], wherein the polypeptide carrier is selected from the group consisting of tetanus toxoid, diphtheria toxoid, pertussis toxoid, [an] a streptococcal immunogenic polypeptide[derived from streptococci], an influenzal immunogenic polypeptide[derived from influenza], [an] a meningococcal immunogenic polypeptide[derived from meningococci], [an] a pneumococcal immunogenic polypeptide[derived from pneumococci], and an *E. coli* immunogenic polypeptide[derived from *E. coli*].

13. (amended) The immunogenic conjugate according to claim 1[3], wherein [the conjugate] hyaluronic acid moieties are [is] directly linked to the immunologically-suitable polypeptide carrier.

14. (amended) The immunogenic conjugate according to claim 1[3], wherein the conjugate elicits antibodies that bind an epitope comprising glucuronic acid or unsaturated glucuronic acid as the nonreducing terminal sugar of a low molecular weight hyaluronic acid moiety.

15. (amended) The immunogenic conjugate according to claim 1[3], wherein the conjugate elicits antibodies that bind capsular hyaluronic acid moieties present in bacteria.

16. (amended) The immunogenic conjugate according to claim 15, wherein the [bacteria] bacterium are group A streptococci or group C streptococci.

19. (amended) A method of preparing a low molecular weight hyaluronic acid moiety – polypeptide conjugate molecule comprising covalently linking low molecular weight

hyaluronic acid [fragments] to an immunologically-suitable polypeptide, wherein about 50% or greater of the low molecular weight hyaluronic acid has [fragments have] a glucuronic acid and/or an unsaturated glucuronic acid residue at the nonreducing terminal.

20. (amended) The method according to claim 19, wherein the method comprising covalently linking a low molecular weight hyaluronic acid to an immunologically-suitable polypeptide comprises reductive amination.

22. (amended) The purified antibody according to claim 21, wherein the low molecular weight hyaluronic acid moieties [fragments] are at least about 4 glycosyl residues in size.

23. (amended) The purified antibody according to claim 22, wherein the hyaluronic acid moieties [fragments] are at least about 4 glycosyl residues and no more than about 40 kD in size.

24. (amended) A pharmaceutical composition effective for treating or inhibiting group A streptococcal or group C streptococcal infection comprising an antibody selected from the group consisting of an antibody elicited by the composition according to claim 17, an antibody according to 21, or an antibody elicited by a low molecular weight hyaluronic acid moiety conjugated to a liposome.

29. (amended) A vaccine [that elicits effective levels of anti-low molecular weight hyaluronic acid antibodies in humans]comprising the immunogenic conjugate according to claim 3, wherein the vaccine elicits an immune response in humans, said immune response comprising production of anti-low molecular weight hyaluronic acid antibodies.

IN THE SPECIFICATION

Please replace the paragraph on page 17, line 16 through page 18, line 3 with the following:

Hyaluronic acid (100 mg, Lifecore lot 1-9062-5) was added to a 10 ml solution of 0.05 N HCl. The mixture was heated at 80 °C for 2 hours, and stirred in order to dissolve the entire solid. The sample was then heated for another 1.5 hours at 100 °C. The depolymerization was monitored by removal of aliquots from the reaction mixture at various times and analysed on a [Bio-Rad] BIO-RAD system (Biologic) equipped with a Superose® 12 HR 10/30 column (Pharmacia). The solution was neutralized with 0.5 N NaOH, then dialysed with a Diaflo® membrane of molecular weight cut-off (MWCO) 3,500 and lyophilized. The product was molecular size fractionated through a Superdex® 200 PG (Pharmacia) column to yield 65 mg of solid product. ^{1}H-NMR analysis of the samples at 500 MHz confirmed the structure of the disaccharide-repeating unit of hyaluronic acid (HA). The average molecular weight of the generated fragment was estimated by size-exclusion chromatography coupled with multiangle laser light scattering photometry (SEC MALLS) to be about 12,000 daltons.

On page 18, lines 14-22, please replace the paragraph as follows:

Hyaluronic acid (100 mg, Lifecore lot 1-9062-5) was dissolved in 20 ml of 10 mM PBS buffer, and the suspension stirred until dissolved. The sample was sonicated with a [Branson] BRANSON sonicator model 450, (sonication settings: Output control: 3; Duty cycle: 50%; temperature: 2 °C) for 18 hours. After dialysis and lyophilization, 57 mg of solid product was recovered. The average molecular weight of the resulting sonicated hyaluronic acid was determined to be 18,000 daltons by SEC-MALLS using a [MiniDawn] MINIDAWN instrument (Wyatt technology, Santa Barbara, CA) and a Superose® 12 HR 10/30 column (Pharmacia). ^{1}H-NMR analysis of the samples at 500 MHz confirmed the structure of the disaccharide-repeating unit of hyaluronic acid.

Please replace the paragraph on page 19, line 16 through page 20, line 5 with the following:

Periodate-oxidized (d.o. 10% and 20%) acid-treated hyaluronic acid (10 mg of each respectively) and purified tetanus toxoid monomer (5 mg for each sample, Statens Serum Institute, Copenhagen, Denmark) were dissolved in 0.5 mL of 0.2 M sodium phosphate, pH 7.4.

Recrystallized sodium cyanoborohydride (10 mg for each sample) was added and the mixture held at room temperature overnight. The progress of the reaction was monitored at various times using a [Bio-Rad] BIO-RAD (Biologic) system equipped with a Superose® 12 HR 10/30 column (Pharmacia). Conjugation of polysaccharide to protein was indicated by a progressive increase of a UV (280 nm) peak eluting in the void volume of the column. After conjugation was completed, 10 mg of $NABH_4$ in 1 ml of 0.1 N NaOH was added to each sample in order to reduce any remaining unconjugated aldehyde. The conjugate was purified by passage over a column (1.6 x 60 cm) of Superdex® 200 PG (Pharmacia) eluting with 10 mM PBS containing 0.01 percent thimerosal. Fractions corresponding to the void-volume peak were pooled and stored at 4 °C. They were designated conjugates 1 and 2 for 10 and 20 percent oxidation in their polysaccharides, respectively.

On page 20, line 14 through page 21, line 4, please replace the paragraph as follows:

Sonicated and periodate-oxidized HA (7 mg of each sample, d.o. 10% and 20%) and purified tetanus toxoid monomer (3.5 mg for each sample) were dissolved in 350 µl of 0.2 M sodium phosphate at pH 7.4. Sodium cyanoborohydride (7 mg for each sample) was added, and the mixtures held at room temperature overnight. The progress of each conjugation reaction was monitored by removal of aliquots from the reaction mixture at various times and subsequent analysis on a [Bio-Rad] BIO-RAD (Biologic) system equipped with a Superose® 12 HR 10/30 column (Pharmacia). Conjugation of polysaccharide to polypeptide was indicated by the progressive increase of a UV absorbing peak (280nm) eluting in the void volume of the column. After conjugation was completed, $NaBH_4$ (10 mg in 1 ml of 0.1 N NaOH for each sample) was added to the reaction mixtures to reduce any remaining unconjugated aldehyde. The conjugates were purified by passage over a Superdex® 200 PG (Pharmacia) column, eluted with 10 mM PBS containing 0.01 percent thimerosal. Fractions corresponding to the void-volume peak were pooled and stored at 4 °C and were designated conjugates 3 and 4 for 10 and 20 percent oxidation in their polysaccharides, respectively.

Please replace the paragraph on page 21, lines 7-15 with the following:

Sonicated and periodate-oxidized hyaluronic acid (20 mg, 20% d.o.) and rPorB (10 mg) were dissolved in 717 µl of 0.25 M HEPES buffer, pH 8.5, containing 0.25 M NaCl and 0.05 percent [Zwittergent] ZWITTERGENT Z 3,14 (Calbiochem, San Diego, CA). Sodium cyanoborohydride (20 mg) was added, and the mixture incubated at 37 °C for 1 day. After the conjugation was completed, 10 mg of sodium borohydride in 1 ml of 0.1 N NaOH was added to the reaction mixture to remove any remaining aldehyde. The conjugate was purified by passage over a column of Superdex® 200 PG (Pharmacia), eluted with 10 mM PBS containing 0.01 percent thimerosal. Fractions corresponding to the void-volume peak, as monitored by UV absorbance at 280 nm, were pooled and stored at 4 °C and labeled as conjugate 5.

On page 22, line 22 through page 23, line 11, please replace the paragraph as follows:

Isolation of the oligosaccharides was performed by anion-exchange chromatography with a [Mono-Q HR] MONO-Q HR 5/5 column (Pharmacia) using a HPLC 1090 (Hewlett Packard 1090 Series II) system equipped with a diode-array detector, a programmable auto-injector, a fraction collector, and the Hewlett Packard Chemstation software program for system control and data acquisition/processing. A step-gradient of sodium chloride in Tris-HCL buffer was used for the separation. Two oligosaccharide fractions corresponding to a dimer (DP2) and a tetramer (DP4) eluting, respectively, between 18 to 26 minutes and between 28 to 31 minutes were collected, lyophilized and desalted using a [Sephadex] SEPHADEX G-10 column (Pharmacia) and deionized water as eluant. The structure of the oligosaccharides was confirmed by examination of their ^{1}H-NMR spectra at 500 MHz. The DP2 oligosaccharide corresponded to Δ4,5-β-GlcU-(1,3)-D-GlcNAc, and the DP4 to Δ4,5-β-GlcU-(1,3)-β-D-GlcNAc-(1,4)-β-D-GlcU-(1,3)-β-D-GlcNAc.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for the timely consideration of this amendment under 37 C.F.R. §§ 1.16 and 1.17, or credit any overpayment to Deposit Account No. 13-4500, Order No. 3842-4050.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition and for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 13-4500, Order No. 3842-4050. A DUPLICATE COPY OF THIS SHEET IS ATTACHED.

Respectfully submitted,

MORGAN & FINNEGAN, L.L.P.

Dated: February 6, 2003

By: _____
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